

made to deliver papain using the biodegradable hydrogels of Hubbell to achieve the beneficial effect of aiding human digestion, as purportedly suggested by Ahmad, and to add surfactants to achieve the beneficial effect of stabilizing the enzyme, as purportedly suggested by Nakayama. The Examiner further contends in this connection that the claimed complex would inherently form during mixing of the components to make the composition allegedly suggested by the combination of the cited prior art references.

Regarding the claimed non-ionic surfactants, the Examiner asserts that one of ordinary skill in the art would use dioleoyl phosphatidylethanolamine (DOPE) or dioleoyl phosphatidylcholine (DOPC) because of their utility for delivering bioactive agents, as purportedly suggested by Weiner.

The above-mentioned rejection, which is non-final in view of the reliance on Weiner et al., constitutes the only ground set forth in the March 22, 2002 Official Action for refusing allowance of this application.

For the reasons set forth below, the §103(a) rejection of claims 1-18 based on the combined disclosures of Hubbell, Ahmad, Nakayama and Weiner is respectfully traversed.

The Examiner's obviousness determination in this case is flawed in several respects. First, the Examiner has disregarded the well-established principle that pending claims must be given the broadest reasonable interpretation which is consistent with the specification and with the interpretation

that those skilled in the art would reach. See §2111 of the Manual of Patent Examining Procedure. Second, this obviousness determination involves hindsight reconstruction of applicants' invention, which directly contravenes the standard of obviousness set forth in 35 U.S.C. §103. Third, with respect to all of the pending claims, the Examiner has overlooked several claim recitations that clearly distinguish these claims over the cited prior art references.

Regarding the first flaw mentioned above, the Examiner has unreasonably interpreted applicants' claims so as to read on the fundamentally different class of polymers disclosed by Hubbell. Applicants' claims call for a composition that includes a supramolecular complex comprising as one of its constituents a block copolymer having at least one nonionic, water soluble segment and at least one polyionic segment. In contrast to applicants' block copolymer-containing composition, Hubbell discloses hydrogels of polymerized and cross-linked macromers, comprising hydrophillic oligomers having biodegradable monomeric or oligomeric extensions which are terminated on free ends with end cap monomers or oligomers capable of polymerization and cross-linking. Hubbell's biodegradable, cross-linked hydrogels are described as being useful for prevention of adhesion formation after surgical procedures, controlled release of drugs and other bioactive species, temporary protection or separation of tissue surfaces, adhering or sealing tissues together and preventing the attachment of cells to tissue surfaces.

In response to the preceding Official Action, it was pointed out that block copolymers, unlike cross-linked hydrogels, are free to defuse in solution. Furthermore, applicants submitted an illustration from L.H. Sperling, Introduction to Physical Polymer Science, J. Wiley & Sons, New York, NY (1992), which shows that a block copolymer is a conjugate of at least two (2) different polymer segments. Such polymers do not include cross-links or other network-type structure. Consistent with this art-recognized understanding of block copolymers is the definition by Tirrel provided at Pages 5-7 of the present specification. This definition includes, e.g. diblock, triblock, multiblock, graft and starblock configurations, none of which have a cross-linked, network structure. Thus, the term "block copolymer" would be understood by those skilled in the art as defining a polymer structure in which at least two (2) different segments, or blocks, are joined end-to-end, and not a cross-linked network as disclosed by Hubbell.

Based on the art-recognized meaning of "block copolymer" as discussed above, the Examiner's contention that applicants' claims do not exclude cross-linked polymers is plainly in error. Block copolymers, by their nature, do not have cross-links. Therefore, it is not necessary for applicants' claims to exclude Hubbell's biodegradable, cross-linked polymers.

The second flaw in the Examiner's position is that it disregards the well-established principles that a determination of obviousness under §103 requires evaluation of the claimed

subject matter as a whole against the facts fairly disclosed in the cited prior art references as a whole, and that it is impermissible to first ascertain factually what applicants did and then view the prior art in such a way as to select from the random facts disclosed therein only those which may be modified and then utilized to reconstruct applicants' invention. In re Shuman, 150 U.S.P.Q. 54, 57 (C.C.P.A. 1966). To the same effect is Ex parte Levengood, 28 U.S.P.Q.2d. 1300 (P.T.O. B.P.A.I. 1993) (Examiner cannot establish obviousness by locating references which describe various aspects of applicants' invention, unless Examiner also provides evidence of motivating force which would impel person skilled in the art to do what applicants have done.) See also, Ex parte Kranz, 19 U.S.P.Q.2d. 1216 (P.T.O. B.P.A.I. 1991).

Despite the clear and long-standing prohibition against reliance on hindsight reconstruction in assessing non-obviousness, that is precisely what the Examiner has done in this case in rejecting claims 1-18 based on the combined disclosures of Hubbell, Ahmad, Nakayama and Weiner. (Not only are these four (4) references drawn from totally unrelated technical fields, the manner in which they have been combined by the Examiner is contrary to express teachings in these references regarding the nature of the inventions described therein.)

The present invention relates to a composition for facilitating delivery of biological agents, which comprises a supramolecular complex including as constituents a block

copolymer, having at least one nonionic, water soluble segment and at least polyionic segment, and at least one charged surfactant having hydrophobic groups. In the complex of the invention, the charge of the surfactant is opposite to that of the polyionic segment of the block copolymer. The prior art references cited as evidence of obviousness, on the other hand, relate to biodegradable, cross-linked hydrogels which are described as being useful as control-release carriers for local application in conjunction with various surgical procedures (Hubbell); compositions for aiding human digestion (Ahmad); stabilization of enzymes used for cleaning of contact lenses (Nakayama); and oil-in-water emulsions for delivery of bioactive agents (Weiner).

In applying the cited references, the Examiner interprets Hubbell (incorrectly, as pointed out above) as disclosing block copolymers for controlled delivery of active agents, such as enzymes, from devices such as microspheres. The Examiner acknowledges that Hubbell does not disclose a charged surfactant as a component of the biodegradable hydrogels described therein. The Examiner then cites not one, but two separate references to make up for the acknowledge deficiency in Hubbell. Thus, Ahmad is cited for its disclosure of a papain-containing digestion aid composition. Based on this disclosure, the Examiner asserts that those of ordinary skill in the art would consider papain as a suitable enzyme for delivery via the biodegradable, cross-linked hydrogels of Hubbell. With the

allegedly obvious combination of Hubbell and Ahmad in hand, the Examiner further contends that it would also have been obvious to add the component admittedly missing from Hubbell, i.e. at least one charged surfactant having a charge opposite to that of the polyionic segment of block copolymer. This additional reliance on Nakayama is based on its disclosure that proteolytic enzymes can be stabilized with various surfactants in formulating a contact lense cleaning solution. It is the combination of papain specifically with the biodegradable, cross-linked hydrogels of Hubbell that warrants the addition of a surfactant for stabilization purposes, according to the Examiner's analysis. The Examiner further relies on Weiner, as suggesting the use of DOPE and DOPC, which are representative of the nonionic surfactants used in certain embodiments of applicants' composition, e.g., as claimed in claims 10 and 11.

The manner in which the Examiner has combined the above-mentioned references is a blatant case of impermissible hindsight, as these references plainly lack the "motivating force which would impel one skilled in the art to do what the patent applicant has done". Ex parte Levengood, supra.

The Ahmad reference emphasizes that the disclosed digestion aid composition consists essentially of "natural organic materials" (see Column 1, line 39; and Column 1, line 68 through Column 2, line 1). The principal ingredients of Ahmad's digestion aid composition are papain (from papaya fruit) to stimulate digestion; hyssop (an herb extract) to soothe and clean

the mouth and throat; and grapefruit to stimulate the generation of saliva (see Column 2, lines 61-64 of Ahmad). Ahmad further discloses that the principal ingredients can be blended in a chewing gum base so that the active ingredients are released to combine with one's saliva and be swallowed to enter the digestive tract over an extended period and in gradual doses.

Although the Examiner contends that it would have been obvious for one of ordinary skill in the art to deliver papain using the microspheres of Hubbell, this argument ignores the fact that there is no mention in Hubbell that the biodegradable cross-linked hydrogel microspheres described therein can be used for oral administration of enzymes, such as papain, or that Hubbell's polymeric materials are otherwise a suitable substitute for a chewing gum base. In fact, there is no mention at all in Hubbell regarding oral administration of the biodegradable, cross-linked hydrogels described therein. Thus, there is absolutely no basis for concluding that those skilled in the art would consider Hubbell's biodegradable, cross-linked hydrogels as being suitable for oral delivery of papain as a digestion aid. Moreover, in view of Ahmad's emphasis that the ingredients of the disclosed digestion aid composition are "natural organic products", one can only wonder as to the source of motivation for combining Ahmad's natural organic products with the macromers, photoinitiator and/or catalyst required to prepare Hubbell's biodegradable, cross-linked hydrogels.

Nakayama is relied on for its disclosure of stabilizing a proteolytic enzyme, such as papain, with a surfactant. Nakayama, however, relates to stabilizing contact lens cleaning agents. Those of ordinary skill in the art would not consider a reference relating to stabilization of contact lens cleaning agents to be of any assistance when the objective being sought is a composition for delivery of therapeutic and diagnostic agents that comprises block copolymers and oppositely charged surfactants. This is particularly true in the present case, as the alleged motivation for incorporating a surfactant with papain, according to Nakayama, is totally absent from both the Hubbell and Ahmad references. Two problems pertaining to proteolytic enzyme inactivation in lens cleaning compositions are addressed by Nakayama. One problem relates to the inactivating effect on proteolytic enzymes produced by water present in surfactants. See Column 2, lines 4-16 of Nakayama. The other problem relates to stabilization of a proteolytic enzyme during lyophilization. See Column 2, lines 23-38 of Nakayama. These problems are purportedly overcome, according to Nakayama, by adding a small amount of surfactant to a proteolytic enzyme in solution (see Column 2, lines 4-8 of Nakayama). Neither of these two instability problems is evident in either the biodegradable, cross-linked hydrogels of Hubbell or the digestion aid composition of Ahmad. Although papain or other proteolytic enzymes may be unstable when formulated as an aqueous contact lens cleaning solution (as described in Nakayama), there is no

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position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggest to one of ordinary skill in the art. In re Wesslau, 147 U.S.P.Q. 391 (C.C.P.A. 1965).

In view of the absence of any motivation or incentive which would lead those of ordinary skill in the art to combine the disclosures of Hubbell, Ahmad, Nakayama and Weiner, for the reasons stated above, it is clear that their combination in formulating the rejection of claims 1-18 under 35 U.S.C. §103(a) is based on impermissible hindsight.

Assuming, for the sake of argument, that the disclosures of Hubbell, Ahmad, Nakayama and Weiner can be combined as proposed by the Examiner (which applicants have vigorously disputed above), the resulting combination nevertheless fails to render obvious the subject matter, as a whole, claimed in claims 1-18. This is the third flaw in the Examiner's position.

Turning first to claim 1 and the claims dependent thereon (2-18), the supramolecular complex is characterized as comprising a block copolymer, having at least one nonionic, water soluble segment and at least one polyionic segment, and at least one charged surfactant having hydrophobic groups, with the charge of the surfactant being opposite to the charge of the polyionic segment of the block copolymer. There is no recognition of this requirement in any of the prior art references of record. Nakayama, which is the reference that allegedly suggests this

feature of applicants' invention, discloses that anionic, amphoteric and nonionic surfactants are equally useful for stabilizing proteolytic enzymes in contact lens cleaning solutions. Anionic surfactants, amphoteric surfactants and nonionic surfactants are not, however, equally useful for forming the supramolecular complex of the present invention. For example, nonionic surfactants would presumably be satisfactory for purposes of Nakayama's invention, but would not be capable of yielding the supramolecular complex called for in claim 1. That being the case, the Examiner is in error in arguing that the claimed complex is inherently formed during mixing of the components from the various cited references. It is well settled that inherency must be a necessary and not merely a possible result, Ex parte Keith, 154 U.S.P.Q. 320 (B.P.A.I. 1966); and that the inherent feature or property must be known or appreciated, In re Spoorman, 150 U.S.P.Q. 449 (C.C.P.A. 1966) (That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown). In this case, applicants' supramolecular complex would not be formed necessarily from the combination of the cited references. As noted above, the nonionic surfactants disclosed by Nakayama, if selected for stabilization based on greater effectiveness, lower cost or any other reason, would not produce the claimed complex. Furthermore, there is no knowledge or appreciation evident in any of the cited references of the desirability of forming a supramolecular complex from the constituents called for in claim

obvious mix

1. Accordingly, the Examiner's inherency argument cannot be maintained.

Regarding claim 3 and the claims dependent thereon (4-14), these claims require that the ratio of the net charge of the surfactant to the net charge of the polyionic segment of the block copolymer is between about 0.01 and about 100. The significance of such a requirement with respect to the vesicle forming capability of the supramolecular complex of the invention is explained in the present specification at page 32, line 2, through page 33, line 16. Here again, there is absolutely no appreciation of this requirement in any of the references cited as evidence of obviousness in this case. Although Hubbell discloses the preparation of microspheres from the biodegradable, cross-linked hydrogels described therein, such microspheres do not require any specific ratio of the net charge of any surfactant to net charge of any polyionic segment for their formation. Indeed, Hubbell does not even disclose a surfactant as a component of the microspheres disclosed therein. This is not at all surprising, as Hubbell's microspheres are made by conventional techniques, as described at Column 10, lines 38-48 of Hubbell. Although Nakayama allegedly provides the requisite motivation to include a surfactant in the papain-containing hydrogels microspheres allegedly suggested by the proposed combination of Hubbell and Ahmad, there is no indication in any of the cited references that the ratio of net charge of the surfactant to that of the polyionic segment of the block

copolymer be in the range specified in claims 3-14.

Applicants' claim 5 and the claims dependent thereon (6-11) all require that the polyionic segment of the block copolymer is polyanionic. In that claim 1 specifies that the charge of the surfactant is opposite to that of the polyionic segment of the block co-polymer, the surfactant component of the composition of claims 5-11 is necessarily a cationic surfactant. The only surfactants mentioned by Nakayama as useful for stabilizing proteolytic enzymes are anionic surfactants, amphoteric surfactants and nonionic surfactants. See Column 2, lines 40-45 and 62-64; and Column 3, lines 1-13 of Nakayama. There is no mention of cationic surfactants anywhere in Nakayama. The conclusion is inescapable, therefore, that the disclosures of Hubbell, Ahmad, Nakayama and Weiner, even if properly combinable, fail to suggest applicants' composition comprising a therapeutic or diagnostic agent and a supramolecular complex, formed of a block copolymer having at least one nonionic, water soluble segment together with at least one polyanionic segment and at least one cationic surfactant, as required in applicants' claims 5-11.

It is noted that at page 5 of the March 22, 2002 Official Action, the Examiner concludes that the ratios or weight percents of applicants' claims are not considered critical, absent evidence showing unexpected and superior results. In this connection, In re Boesch, 205 U.S.P.Q. 205 (C.C.P.A. 1980) is cited for the proposition that it is within the skill of the art

to select optimal parameters, such as ratios or weight percents of components in order to achieve a beneficial effect. The facts in Boesch, however, are readily distinguishable from those of the present case. The claims on appeal in Boesch were directed to a nickel-based alloy in which certain of the elements were balanced, according to an equation, to provide a claimed parameter referred to as N_v (i.e., the average electron vacancy concentration per atom in the matrix of the alloy) so as to fall within prescribed limits. The two references cited as evidence of obviousness in Boesch each disclosed an alloy having the exact same constituents (has the claims on appeal and the ranges of constituents overlapped. Moreover, it was specifically found in Boesch that the prior art would have suggested the kind of experimentation necessary to achieve the claimed composition, including the proportional balancing specified by the appellants' N_v equation.

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In the present case, by contrast, not one of the cited references discloses all of the constituents of applicants' composition. Nor is there any suggestion in any of the cited references of the requirement of claims 1-18 that a block copolymer have a polyionic segment that is complexed with an oppositely charged surfactant, or the requirement of claims 3-14 that a ratio of the net charge of the surfactant to the net charge of the polyionic segment of the block copolymer is between about 0.01 and about 100 or the requirement of claims 5-11 that the polymer segment of the block copolymer is polyanionic and the

surfactant is cationic. Thus, the prior art references cited in Boesch were directly related to Boesch's invention, were applied without any reliance on hindsight and unquestionably established that the appealed claims were *prima facie* obvious, whereas the prior art references cited in this case are from diverse fields unrelated to applicants' invention, which cannot be combined without the use of impermissible hindsight, and therefore, plainly fail to establish *prima facie* obviousness.

For all of the above reasons, the combined disclosures of Hubbell, Ahmad, Nakayama and Weiner fail to provide a proper basis for concluding that the subject matter of claims 1-18, as a whole, is *prima facie* obvious. Therefore, no evidence of surprising or unexpected result need be presented. In re Lunsford, 148 U.S.P.Q. 721 (C.C.P.A. 1966).

The Examiner is correct in assuming at page 6 of the March 22, 2002 Official Action, that the subject matter of the various claims was commonly owned at the time the invention covered thereby was made.

In view of the foregoing remarks, it is respectfully urged that the rejection set forth in the March 22, 2002 Official Action be withdrawn and that this application be passed to issue and such action is earnestly solicited.

DANN DORFMAN HERRELL and
SKILLMAN, P.C.
Attorneys for Applicant

By

Patrick J. Hagan
Patrick J. Hagan
Registration No. 27,643

PJH:ksk